Received: 23 March 2022 | Revised: 29 January 2023 | Accepted: 3 February 2023

DOI: 10.1111/aogs.14536

ORIGINAL RESEARCH ARTICLE

Does induction of labor at 41 weeks (early, mid or late) improve birth outcomes in low-risk pregnancy? A nationwide propensity score-matched study

Anita C. J. Ravelli[1,2,3] | Joris A. M. van der Post[2,4] | Christianne J. M. de Groot[2,4] | Ameen Abu-Hanna[1,3] | Martine Eskes[1]

[1]Department of Medical Informatics, AmsterdamUMC Location University of Amsterdam, Amsterdam, The Netherlands

[2]Department of Obstetrics and Gynecology, AmsterdamUMC Location University of Amsterdam, Amsterdam, The Netherlands

[3]Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

[4]Amsterdam Reproduction and Development Research Institute, Amsterdam, The Netherlands

Correspondence
Martine Eskes, Department of Medical Informatics/Obstetrics & Gynecology, Amsterdam UMC Location University of Amsterdam, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands.
Email: m.eskes@amsterdamumc.nl

Abstract

Introduction: This study aimed to assess whether induction of labor at 41 weeks of gestation improved perinatal outcomes in a low-risk pregnancy compared with expectant management.

Material and methods: Registry-based national cohort study in The Netherlands. The study population comprised 239 971 low-risk singleton pregnancies from 2010 to 2019, with birth occurring from 41+0 to 42+0 weeks. We used propensity score matching to compare induction of labor in three 2-day groups to expectant management, and further conducted separate analyses by parity. The main outcome measures were stillbirth, perinatal mortality, 5-min Apgar <4 and <7, neonatal intensive care unit (NICU) admissions ≥24 h, and emergency cesarean section rate.

Results: Compared with expectant management, induction of labor at 41+0 to 41+1 weeks resulted in reduced stillbirths (adjusted odds ratio [aOR] 0.15, 95% confidence interval [CI] 0.05–0.51) in both nulliparous and multiparous women. Induction of labor increased 5-min Apgar score <7 (aOR 1.30, 95% CI 1.09–1.55) and NICU admissions ≥24 h (aOR 2.12, 95% CI 1.53–2.92), particularly in nulliparous women, and increased the cesarean section rate (aOR 1.42, 95% CI 1.34–1.51). At 41+2–41+3 weeks, induction of labor reduced perinatal mortality (aOR 0.13, 95% CI 0.04–0.43) in both nulliparous and multiparous women. The rate of 5-min Apgar score <7 was increased (aOR 1.26, 95% CI 1.06–1.50), reaching significance in multiparous women. The cesarean section rate increased (aOR 1.57, 95% CI 1.48–1.67) in both nulliparous and multiparous women. Induction of labor at 41+4 to 41+5 weeks reduced stillbirths (aOR 0.30, 95% CI 0.10–0.93). Induction of labor increased rates of 5-min Apgar score <4 (aOR 1.61, 95% CI 1.01–2.56) and NICU admissions ≥24 h (aOR 1.52, 95% CI 1.08–2.13) in nulliparous women. Cesarean section rate was increased (aOR 1.47, 95% CI 1.38–1.57) in nulliparous and multiparous women.

Abbreviations: aOR, confidence interval adjusted odds ratio; CI, confidence interval; CS, cesarean section; IOL, induction of labor; MAS, meconium aspiration syndrome; NICU, neonatal intensive care unit; NNT, needed to treat; RCT, randomized controlled trial.

Conclusions: At 41+2 to 41+3 weeks, induction of labor reduced perinatal mortality, and in all 2-day groups at 41 weeks, it reduced stillbirths, compared with expectant management. Low 5-min Apgar score (<7 and <4) and NICU admissions ≥24 h occurred more often with induction of labor, especially in nulliparous women. Induction of labor in all 2-day groups coincided with elevated cesarean section rates in nulliparous and multiparous women. These findings pertaining to the choice of induction of labor vs expectant management should be discussed when counseling women at 41 weeks of gestation.

KEYWORDS

adverse neonatal outcome, emergency cesarean section, induction of labor, prolonged pregnancy, propensity score matching

1 | INTRODUCTION

Infants born following a prolonged gestation beyond 41 weeks have progressively higher risks of mortality and morbidity.[1–4] Post-term pregnancy (42+0 weeks or more) increases the risk for babies, including a greater risk of stillbirth, death shortly after birth and adverse perinatal outcome.[5–9] Therefore, guidelines recommend induction of labor (IOL) at 42+0 weeks, which is now considered general practice in most European countries.[10] However, the optimal timing of IOL vs expectant management for women at 41 weeks or earlier is still unclear and requires further investigation.[11–14]

The recently updated Cochrane systematic review of randomized controlled studies on IOL by Middleton et al.[12] included 20 studies investigating outcomes at 41 weeks. Compared with expectant management until 42 weeks, IOL at 41 weeks significantly reduced perinatal mortality, neonatal intensive care (NICU) admissions, and severe neonatal morbidity, although the absolute rates of adverse outcomes were small.

Due to the small number of cases with adverse outcomes at 41 weeks, randomized controlled trials (RCTs) tend to lack the statistical power to study separate outcome measurements and perform analysis by parity. Two RCTs and one individual participant data meta-analysis on IOL at 41 weeks of gestational age have recently been published.[15–17] A randomized controlled trial (INDEX) in the Netherlands found that the absolute risk of severe adverse perinatal outcomes was 1.7% in the induction group and 3.1% in the expectant group.[16] No difference in cesarean section (CS) rate was found. A randomized trial in Sweden (SWEPIS) in women with a low-risk singleton pregnancy showed a statistically higher perinatal mortality rate in the expectant management group vs IOL at 41 weeks of gestation, without differences in cesarean delivery.[17] A further individual participant data analysis concluded that IOL at 41 weeks significantly reduced the composite outcome of perinatal mortality and severe morbidity compared with expectant management until 42 weeks without increasing the CS rate in nulliparous women.[15] Reliable information for IOL of multiparous women at 41 weeks is still lacking. In addition, the optimal time for IOL in week 41 on specific day intervals is unknown.

Key message

Induction of labor in a low-risk population at 41 weeks was independently associated with reduced perinatal deaths but increased rates of lower 5-min Apgar scores (<4 and <7) and NICU admissions, and higher emergency CS rates as compared with expectant management in all 2-day groups.

The purpose of this study was to answer the following research questions using propensity score matching in a large national cohort:

- Does IOL at 41 weeks at specific 2-day intervals reduce perinatal mortality and severe neonatal morbidity compared to expectant management at 41 weeks?
- What are the stratified results for nulliparous and multiparous women?
- Does IOL affect maternal outcomes, such as instrumental delivery and CS rates, compared with expectant management at 41 weeks?

2 | MATERIAL AND METHODS

2.1 | Study design

This was a nationwide registry-based cohort study.

2.2 | Setting

In the Netherlands, women with low-risk term pregnancies (37+0 to 41+6 weeks of gestation) are managed under the care of independent midwives or general practitioners (primary/midwifery-led care) during pregnancy, labor and delivery. When complications (threaten to) occur, women are referred to an obstetrician (specialist care). Gestational age

is routinely determined by ultrasound dating scans early in the second trimester (approximately 12 weeks of gestational age).

Expectant management, which includes assessment of the fetal condition with sonographic examination and electronic fetal monitoring during one or two visits between 41+0 and 42+0 weeks of gestation, is a common practice for low-risk pregnancies. Induction is performed at the mother's request between 41+0 and 42+0 weeks. In the Netherlands, IOL is recommended by the guidelines and is a standard procedure after 42+0 weeks.[18]

2.3 | Data source

In this study, we used data from the National Perinatal Registry (Perined; www.perined.nl). Perined is a linked database of all perinatal caregivers (midwives, general practitioners, obstetricians and neonatologists).[19,20]

2.4 | Population

We extracted data of singleton deliveries during the period 2010–2019 with low-risk, defined as women without elective CS, women without a history of CS, non-cephalic presentation of the fetus, and children without congenital anomalies or small-for-gestational-age infants (below 5th percentile birthweight), and women without hypertensive disorders, diabetes mellitus or gestational diabetes. Congenital anomalies were classified as major and minor congenital anomalies defined by midwives, obstetricians and neonatologists in the general categories of anomalies by organ systems (www.perined.nl). We further excluded women for whom the method of labor onset was not clear in the registration (Figure 1). In the three IOL groups, the child had to be alive at the start of labor; therefore, antepartum deaths were excluded in these 2-day induction groups. This is because, in the event of antepartum death, IOL is the main delivery path, and the perinatal database does not provide information about the moment of antepartum death.

2.5 | Exposure

We subdivided the study group into three 2-day subsamples: early, mid and late (Table 1). We first analyzed group 1 (G1) IOL at 41+0 and 41+1 weeks (day 287–288) and compared these results with those of expectant management from 41+0 to 42+0 (287–294 days). Then, we repeated this analysis with the G2 group IOL (41+2 and 41+3, 289–290 days), which we compared with expectant management from 41+2 to 42+0 (289–294 days). G3 group IOL (41+4 and 41+5, 291–292 days) was subsequently compared with expectant management from 41+4 to 42+0 (291–294 days). Expectant management includes the first 2 days with spontaneous start of labor and the following days until 42+0 weeks of all ongoing pregnancies with spontaneous start of labor or induction.

2.6 | Outcomes

The main neonatal outcome measurements were stillbirth, perinatal mortality (stillbirth or neonatal mortality within 28 days), 5-min Apgar score <4 and 5-min Apgar score <7, and NICU admission ≥24 h. Secondary neonatal outcomes included meconium aspiration syndrome (MAS) and neonatal admission for asphyxia, defined as admission asphyxia and/or admission for cooling treatment for asphyxia and/or admission for ischemic asphyxia and/or convulsions and/or intraventricular bleeding and/or encephalopathy. Adverse neonatal outcomes were defined as perinatal mortality (stillbirth or neonatal mortality <28 days) and/or 5-min Apgar <4 and/or NICU admission ≥24 h and/or MAS and/or neonatal admission for asphyxia. When a child showed more than one adverse event, this was counted as one adverse outcome.

Maternal outcome measurements included instrumental vaginal delivery and emergency CS rates. A secondary or emergency CS is performed after the start of labor in cases of complications during labor or delivery. This is in contrast to primary (elective) CS, which is performed before the start of labor. Secondary CS rates were further described as emergency CS rates.

2.7 | Statistical analyses

We analyzed outcomes in the three different IOL groups and compared the results with those of the expectant management groups within 41 weeks of gestation (Table 1). Specifically, propensity score matching was applied to match the characteristics of women who received IOL with those of women who underwent expectant management. By doing this, the effect of possible confounding by indication was minimized. The propensity score approach attempts to balance the maternal characteristics of women who receive induction with those in the expectant management reference group. First, we performed a pre-analysis of non-matched data. The variables used to calculate the propensity score were selected based on the literature and availability in the national registry.[1,4,5,7,16,21] The matching variables used for IOL included late start of antenatal care (≥15 weeks of gestation), parity, ethnicity, infertility treatment (ART), maternal age, socioeconomic status quintiles, year of birth (2010–2019), birthweight percentile in five groups (p5-p9, p10-p49, p50-79, p80-p89, p90-p100), and male sex of the child. We further matched the induction characteristics of the birth units (units with low inductions in week 41 [<40%], units with mean induction rates [40%–45%] and units with a high percentage of inductions [>45%]). Missing values in the matching variables were rare and were treated by single imputation. Continuous and categorical variables were used as matching variables in the propensity score analysis, which was performed with 1:1 matching. The nearest neighbor matching algorithm was executed separately for each of the three study groups (G1, G2 and G3).

For each of the three study groups, we tested differences in neonatal and maternal outcome measurements between IOL and

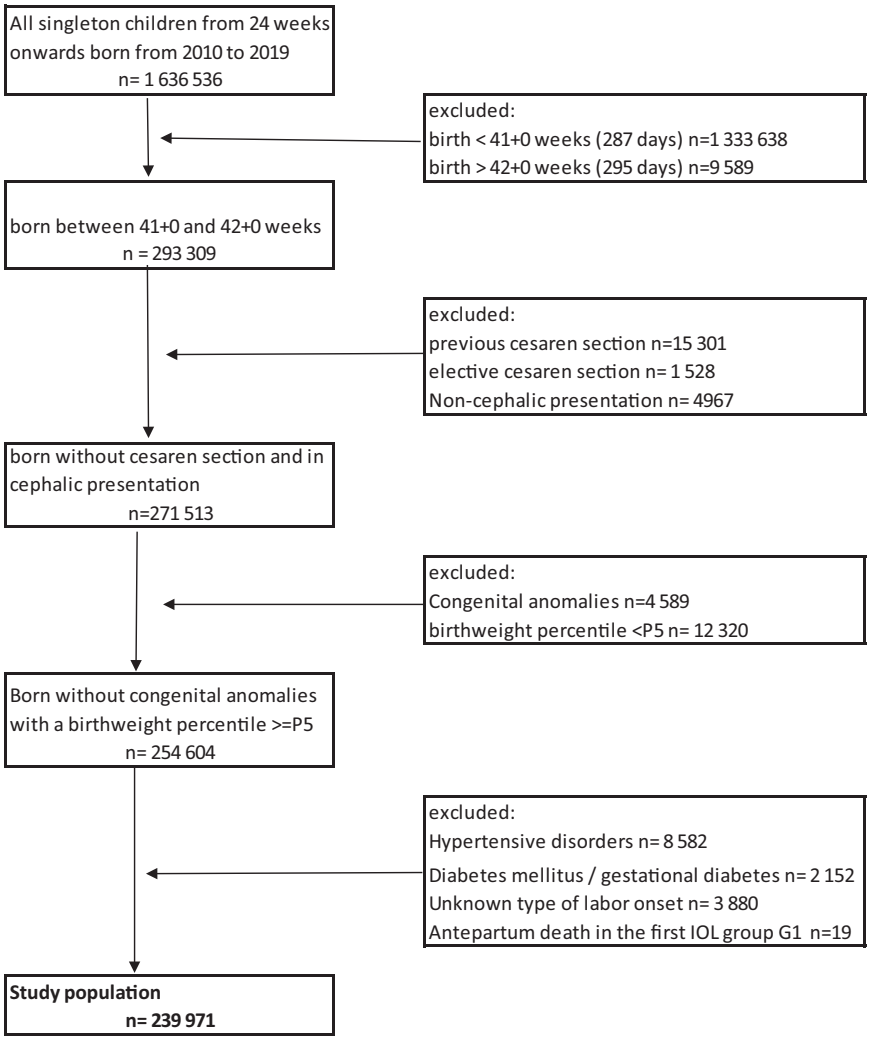

FIGURE 1 Flow chart of the study population.

expectant management before and after matching using chi-square and logistic regression analyses. Finally, the analysis was conducted according to parity (nulliparous or multiparous).

The overall propensity score between IOL and expectant management was calculated and tested before and after matching using the *t*-test. The covariate balance in the matched samples was tested for all variables used in the matching. We further used the *t*-test for continuous variables and chi-square test for categorical variables before and after matching, and we applied the standardized mean differences.

The crude and adjusted odds ratios (aOR) with a 95% confidence interval (CI) were calculated using logistic regression for the outcome differences between IOL and expectant management. Adjustment of the odds ratios was only performed for parity in the total population. In addition, based on the outcomes after matching, we performed a doubly robust estimation by adjusting for any matching variables (eg ethnicity, fertility treatment, maternal age, SES or fetal gender) that were not fully balanced. This was performed for all outcome variables except mortality, for which the sample size was too small.

The number needed to treat (NNT) was calculated for stillbirth or perinatal death as the inverse of the absolute risk reduction between induction and expectant management (1/absolute risk reduction).

All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) and R and R Studio (version 4.0.3. using the Matchit package).[22]

2.8 | ETHICS STATEMENT

Approval for this study was granted by the Committee of Research and Ethics of Perined (Approval no. 2020-36) on October 13, 2020.

3 | RESULTS

We included 239 971 low-risk pregnancies from 41+0 weeks (287 days) to 42+0 weeks (294 days) from the singleton study population (n = 1 636 536). The flow chart in Figure 1 shows the different exclusion groups, including antepartum deaths (n = 19), in the first IOL group. The mean maternal age was 30.6 years and the mean birthweight was 3782 g.

The IOL rate was 29.7%, and the induction rate significantly increased over the gestational age of 41 weeks. The induction rate was 20.1% at 41+0 (day 287) and 67.7% at 42+0 (day 294).

TABLE 1 Induction of labor vs expectant management in different propensity score-matched groups at 41 weeks of gestation.

	Induction of labor		Expectant management		Original			Propensity matched		
	Gestational age			until	expectant management	Induction of labor	Total	expectant management	Induction of labor	Total
	Weeks + days	days	days	weeks + days	*n*	*n*	*n*	*n*	*n*	*n*
Group 1 G1	41+0 to 41+1	287–288	287–294	42+0	218008	21963	239971	21963	21963	43926
Group 2 G2	41+2 to 41+3	289–290	289–294	42+0	123903	17565	141468	17565	17565	35130
Group 3 G3	41+4 to 41+5	291–292	291–294	42+0	57220	15749	72969	15749	15749	31498

The overall incidence of adverse neonatal outcomes at 41 weeks of gestation was low for perinatal mortality (0.10%), 5-min Apgar <4 (0.17%) and 5-min Apgar <7 (1.3%). The incidence rates over 41 weeks were 11.5% for instrumental delivery and 10.3% for emergency cesarean delivery, which were higher in nulliparous women than in multiparous women (20.0% and 17.4%, respectively; Table S1).

Table 1 shows the three different study groups (G1–G3), each demarcated by a 2-day interval, and women with IOL compared with women with expectant management.

IOL at 41+0 to 41+1 weeks (287–288 days) (G1) (n = 239 971) compared with expectant management until 42+0 (day 294) showed that stillbirth significantly decreased (aOR 0.15, 95% CI 0.05–0.51) but perinatal mortality did not (aOR 0.55, 95% CI 0.29–1.04). Overall, 1250 inductions were needed (NNT) to prevent one stillbirth.

IOL at 41+0 to 41+1 weeks significantly increased the rates of 5-min Apgar score <7 (aOR 1.30, 95% CI 1.09–1.55) and NICU admissions ≥24 h (aOR 2.12, 95% CI 1.53–2.92). In addition, admission for asphyxia increased after IOL, as did adverse neonatal outcomes.

Parity analysis showed that stillbirth was significantly decreased in nulliparous and multiparous women. The adverse effects of low Apgar score <7, NICU admission and adverse neonatal outcomes were significantly increased only among nulliparous women (Table 2). The emergency CS rate was significantly increased (aOR 1.42, 95% CI 1.34–1.51) after IOL, but only for nulliparous women. Propensity scores after matching were comparable (p = 0.62). The characteristics of the women and children in G1 before and after matching are described in Table S2. Because there were still small differences in ethnicity and fertility treatment, we further adjusted for these factors, besides parity, when obtaining the adjusted odds ratios.

In the IOL at 41+2 to 41+3 weeks (G2) (289–290 days), we enrolled 141 468 infants after excluding 20 antepartum deaths in the IOL group. As compared with expectant management until 42+0 (day 294), IOL at 41+2 to 41+3 weeks resulted in a reduced risk of perinatal mortality (three deaths of 17 565 vs. 23 deaths out of 17 565 [0.02% vs. 0.13%], p < 0.0001; aOR 0.13, 95% CI 0.04–0.43), and reduced the risk of stillbirth (Table 3). A total of 909 inductions were required (NNT) to prevent one perinatal death. After IOL, there was also a significant increase in 5-min Apgar score <7 (aOR 1.26, 95% CI 1.06–1.50). Analysis by parity showed that perinatal mortality was significantly lower in nulliparous and multiparous women, and the 5-min Apgar score <7 was increased in multiparous women. The emergency CS rate was significantly increased after IOL (aOR 1.57, 95% CI 1.48–1.67) for both nulliparous and multiparous women. Instrumental delivery increased after IOL (aOR 1.10, 95% CI 1.03–1.17) but this difference was only significant for nulliparous women (aOR 1.11, 95% CI 1.03–1.19 and aOR 1.05, 95% CI 0.90–1.23, respectively).

Matching resulted in comparable propensity scores between the IOL and expectant groups (p = 0.71). The characteristics of the women and children in G2 before and after matching are shown in Table S3. Because there were still small differences in ethnicity and

TABLE 2 Outcomes of G1 induction at 41+0 to 41+1 weeks (287–288 days) vs expectant management until 42+0 (294 days) after propensity-score matching.

Group G1 induction: 287–288			Propensity matched						Induction of labor		Induction of labor	
Reference: 287–294	Expectant management		Expectant management		Induction of labor		Before matching	After matching	Crude odds ratio		Adjusted #1odds ratio	
	218008		21963		21963		239971	43926	OR	(95% CI)	OR	(95% CI)
Total	*n*	%	*n*	%	*n*	%	*p*-value	*p*-value				
Perinatal mortality	218	0.10%	27	0.12%	15	0.07%	0.15	0.064	0.55	(0.30–1.04)	0.55	(0.29–1.04)
Stillbirth	144	0.07%	20	0.09%	3	0.001%	**0.0028**	**0.0004**	**0.15**	**(0.05–0.50)**	**0.15**	**(0.05–0.51)**
Neonatal mortality <28	74	0.03%	7	0.03%	12	0.05%	0.12	0.25	1.72	(0.68–4.36)	1.70	(0.70–4.32)
5-min Apgar <4	368	0.17%	25	0.11%	34	0.15%	0.63	0.24	1.36	(0.81–2.28)	1.32	(0.79–2.22)
5-min Apgar <7	2807	1.29%	222	1.01%	290	1.32%	0.68	**0.0025**	**1.31**	**(1.10–1.56)**	**1.30**	**(1.09–1.55)**
MAS	342	0.16%	20	0.09%	21	0.10%	**0.03**	0.88	1.05	(0.57–1.94)	1.04	(0.56–1.91)
NICU admission (≥24 h)	847	0.39%	55	0.25%	117	0.53%	**0.0013**	**<0.0001**	**2.13**	**(1.55–2.94)**	**2.12**	**(1.53–2.92)**
Instrumental delivery	25131	11.5%	2430	11.1%	2453	11.2%	0.11	0.73	1.01	(0.95–1.07)	1.01	(0.95–1.08)
Emergency cesarean section	21680	9.94%	2194	10.0%	2953	13.5%	**<0.0001**	**<0.0001**	**1.40**	**(1.32–1.48)**	**1.42**	**(1.34–1.51)**
Admission asphyxia	993	0.46%	62	0.28%	91	0.41%	0.39	**0.019**	**1.47**	**(1.06–2.03)**	**1.46**	**(1.06–2.02)**
Adverse neonatal outcome	1845	0.85%	131	0.60%	198	0.90%	0.40	**0.0002**	**1.52**	**(1.22–1.89)**	**1.51**	**(1.21–1.88)**
Predicted probability	0.2837	0.16	0.4169	0.16	0.4176	0.16	**<0.0001**	0.62				
Group G1 Induction: 287–288									**Induction of labor**		**Induction of labor**	
Reference: 287–294	**Expectant management**		**Expectant management**		**Induction of labor**		**Before matching**	**After matching**	**Crude odds ratio**		**Adjusted #2odds ratio**	
Nulliparous	**110565**		**10110**		**10109**				**OR**	**(95% CI)**	**OR**	**(95% CI)**
Perinatal mortality	145	0.13%	17	0.17%	11	0.11%	0.55	0.26	0.65	(0.30–1.38)	0.63	(0.30–1.35)
Stillbirth	89	0.08%	11	0.11%	2	0.02%	**0.03**	**0.013**	**0.18**	**(0.04–0.82)**	**0.18**	**(0.04–0.80)**
Neonatal mortality <28 days	56	0.05%	6	0.06%	9	0.09%	0.11	0.44	1.50	(0.53–4.22)	1.46	(0.52–4.13)
5-min Apgar <4	287	0.26%	16	0.16%	26	0.26%	0.96	0.12	1.63	(0.87–3.03)	1.60	(0.86–2.98)
5-min Apgar <7	2103	1.90%	139	1.37%	202	2.00%	0.50	**0.0006**	**1.46**	**(1.18–1.82)**	**1.46**	**(1.18–1.80)**
MAS	284	0.26%	16	0.16%	15	0.15%	**0.04**	0.86	0.94	(0.46–1.90)	0.91	(0.45–1.84)
NICU admission (≥24 h)	618	0.56%	33	0.33%	89	0.88%	**<0.0001**	**<0.0001**	**2.71**	**(1.82–4.05)**	**2.67**	**(1.78–3.98)**

(Continues)

TABLE 2 (Continued)

Group G1 Induction: 287–288									Induction of labor		Induction of labor	
Reference: 287–294	Expectant management		Expectant management		Induction of labor		Before matching	After matching	Crude odds ratio		Adjusted #2odds ratio	
Instrumental delivery	22169	20.1%	1940	19.2%	2003	19.8%	0.57	0.26	1.04	(0.97–1.12)	1.04	(0.97–1.11)
Emergency cesarean section	18607	16.8%	1678	16.6%	2372	23.5%	**<0.0001**	**<0.0001**	**1.54**	**(1.44–1.65)**	**1.52**	**(1.42–1.63)**
Admission asphyxia	760	0.69%	42	0.42%	57	0.56%	0.15	0.13	1.36	(0.91–2.03)	1.35	(0.91–2.01)
Adverse neonatal outcome	1365	1.23%	82	0.81%	140	1.38%	0.19	**<0.0001**	**1.72**	**(1.31–2.26)**	**1.69**	**(1.29–2.23)**
Multiparous	**107443**		**11853**		**11854**							
Perinatal mortality	73	0.07%	10	0.08%	4	0.03%	0.16	0.11	0.40	(0.13–1.28)	0.40	(0.13–1.29)
Stillbirth	55	0.05%	9	0.08%	1	0.01%	**0.04**	**0.011**	**0.11**	**(0.01–0.88)**	**0.11**	**(0.01–0.89)**
Neonatal mortality <28 days	18	0.02%	1	0.01%	3	0.03%	0.51	0.32	3.00	(0.31–28.8)	3.00	(0.31–28.8)
5-min Apgar <4	81	0.08%	9	0.08%	8	0.07%	0.76	0.81	0.90	(0.34–2.30)	0.88	(0.34–2.27)
5-min Apgar <7	704	0.66%	83	0.70%	88	0.74%	0.27	0.70	1.06	(0.79–1.43)	1.06	(0.78–1.43)
MAS	58	0.05%	4	0.03%	6	0.05%	0.88	0.53	1.50	(0.42–5.32)	1.47	(0.42–5.22)
NICU admission (≥24 h)	229	0.21%	22	0.19%	28	0.40%	0.60	0.40	1.27	(0.73–2.28)	1.26	(0.72–2.20)
Instrumental delivery	2962	2.76%	490	4.13%	450	3.80%	**<0.0001**	0.18	0.92	(0.80–1.04)	0.92	(0.80–1.04)
Emergency cesarean section	3073	2.86%	516	4.35%	581	4.90%	**<0.0001**	**0.044**	**1.13**	**(1.003–1.28)**	1.12	(0.99–1.27)
Admission asphyxia	233	0.22%	20	0.17%	34	0.29%	0.13	0.056	1.70	(0.98–2.96)	1.69	(0.97–2.93)
Adverse neonatal outcome	480	0.45%	49	0.41%	58	0.49%	0.51	0.38	1.18	(0.81–1.73)	1.17	(0.80–1.72)

Note: Adjusted G1 #1 for parity, ethnicity, ART and age (except for mortality outcome because of low numbers). Adjusted #2 for ethnicity, ART and maternal age (except for the mortality outcome). Adverse neonatal outcome = perinatal mortality (stillbirth and neonatal death <28 days), and/or 5-min Apgar <4, and/or NICU admission ≥24 h, and/or meconium aspiration syndrome (MAS), and/or admission asphyxia (cooling treatment for asphyxia, and/or ischemic asphyxia, and/or convulsions, and/or intraventricular bleeding, and/or encephalopathy).

Note: Significant values in bold.

Abbreviations: CI, confidence interval; MAS, meconium aspiration syndrome; NICU, neonatal intensive care unit.

fertility treatment, we further adjusted for these factors, in addition to parity, when analyzing the adjusted odds ratios in G2 in the total population.

The IOL at 41+4 to 41+5 weeks (G3) (291–292 days) included 72 969 infants after exclusion of 13 antepartum deaths in the IOL group. Compared with expectant management until 42+0 (day 294), IOL at 41+4 to 41+5 weeks showed differences in neonatal outcomes, and stillbirths were reduced (aOR 0.30, 95% CI 0.10–0.93). A total of 2000 inductions (NNT) were required to prevent one stillbirth. The rate of 5-min Apgar score <4 was increased (aOR 1.61, 95% CI 1.01–2.56) and NICU admissions were also higher (aOR 1.52, 95% CI 1.08–2.13); both were significantly increased in nulliparous women.

Significantly higher emergency CS rates were observed after IOL at 41+4 to 41+5 weeks (aOR 1.47, 95% CI 1.38–1.57) and these were significantly increased in nulliparous and multiparous women. Instrumental deliveries increased with IOL (aOR 1.08, 95% CI 1.01–1.15) (Table 4).

The characteristics of the women and children in G3 before and after matching are described in Table S4. Because there were still small differences in ethnicity and weeks of care, we further adjusted for these factors, in addition to parity, when obtaining the adjusted odds ratios.

4 | DISCUSSION

In all day groups at 41 weeks, IOL reduced stillbirth compared with expectant management. At 41+2 to 41+3 weeks, IOL reduced perinatal mortality in nulliparous and multiparous women. More children with low 5-min Apgar scores and more NICU admissions occurred with IOL, especially in nulliparous women. IOL in all 2-day groups coincided with an elevated CS rate for both nulliparous and multiparous women.

NNT analysis showed that in G1, 1250 inductions were needed to prevent one stillbirth; in G2, 909 inductions were needed to prevent one perinatal death; and in G3, 2000 inductions were needed to prevent one stillbirth.

A major strength of our study was the use of a national registry database with large numbers in the general population. In this recent cohort, IOL at 41 weeks of gestation was and is not yet a common practice as in other European and Western countries.[23] Another strength of this cohort study is the application of the propensity score matching method. RCTs that previously investigated this study question lacked the statistical power to separate neonatal outcomes and to perform analysis by parity due to the small number of adverse outcome cases at 41 weeks. RCTs on IOL and expectant management at 41 weeks may provide results that are not generalizable, as more than 70% of the eligible women refused to participate in these trials.[16,17]

Propensity score analysis minimized the effect of possible confounding by indication in the IOL group, as each characteristic of a woman with IOL was matched with a woman with the same characteristics in the expectant management group. Induction can be performed when complications (threaten to) occur, or at the request of the mother. Unfortunately, we lacked the information required to analyze the influence of these unmeasured factors.

In our study, we used 2-day intervals to separate patients in a manner similar to that used by Pyykonen et al.[21] with 3-day intervals. Another recent study on risks at 41 weeks did not use propensity score matching but adjusted for induction.[4] That study found a higher incidence of neonatal morbidity and emergency CS at 41+4 to 42+0 weeks than for births at 41+0 to 41+3 weeks.

This cohort study was limited compared with RCTs in that only the IOL on a specific day could be used, not the intended IOL. The cohort analyzed in the present study included all births at 41+0 to 42+0 weeks of gestational age in the Netherlands (with 98% completeness) and included relevant potential confounders, except for smoking and body mass index (BMI). The time (day, hour) of antepartum death was not registered in the national registry and the umbilical pH value was not routinely measured; therefore, these data could not be used.

Antepartum deaths were included in the expectant group but not in the IOL groups. Thus, stillbirth and perinatal mortality may have been overestimated in the expectant group, as some infants who died before the start of labor were included.

Induction resulted in a reduction in stillbirth in all 2-day groups at 41 weeks of gestation compared with expectant management, in addition to a reduction in perinatal mortality in the IOL group from 41+2 to 41+3 weeks. The Dutch randomized trial INDEX showed that inductions resulted in a significant difference in adverse perinatal outcomes, but not in perinatal mortality, compared with expectant management.

We further found that after induction in week 41, compared with expectant management, there were more NICU admissions ≥24 h and more adverse outcomes with 5-min Apgar <7 and 5-min Apgar <4. This agrees with the results of some studies examined in the systematic reviews by Middleton et al.[12] and Roach et al.,[24] whereas other studies in the same reviews showed decreased risks for NICU admission and Apgar <7 after IOL.

An important finding in our study is the increased risk of emergency CS rates after IOL in any day group at 41 weeks. This finding agrees with that of several observational studies.[23,25] However, the results of our study conflict with those of two systematic reviews that concluded that IOL at week 41 had even lower emergency CS rates than did expectant management.[26,27] Recent RCTs have shown no increase in CS after IOL at 41 weeks.[15–17,28] Trials on IOL at 41 weeks of gestation, where less than 70% of eligible women agreed to participate, are possibly not generalizable. Future research based on matched observational studies with a large number of observations, such as the study by Pyykonen et al.,[21] may further explain the differences in CS rate outcomes between RCTs and cohort studies. It is also possible that trials generate more vigilance during IOL and in expectant management groups, and CS rates are therefore not comparable with daily practice.[16,17,29]

TABLE 3 Outcomes of G2 induction at 41+2 to 41+3 weeks (289–290 days) vs expectant management until 42+0 (294 days) after propensity score matching.

Group G2 Induction: 289–290			Propensity matched						Crude odds ratio		Induction of labor	
Reference: 289–294	Expectant management		Expectant management		Induction of labor		Before matching	After matching	Crude odds ratio		Adjusted #1 odds ratio	
	123 903		17 565		17 565		141 468	35 130	OR	(95% CI)	OR	(95% CI)
Total	*n*	%	*n*	%	*n*	%	*p*-value	*p*-value				
Perinatal mortality	141	0.11%	23	0.13%	3	0.02%	**0.0002**	**<0.0001**	**0.13**	**(0.04–0.43)**	**0.13**	**(0.04–0.43)**
Stillbirth	89	0.07%	18	0.10%	0	0.00%	**0.0004**	**<0.0001**	N.A.		N.A.	
Neonatal mortality <28 days	52	0.04%	5	0.03%	3	0.02%	0.11	0.48	0.60	(0.14–2.51)	0.61	(0.15–2.55)
5-min Apgar <4	227	0.18%	30	0.17%	41	0.23%	0.15	0.19	1.37	(0.85–2.19)	1.32	(0.82–2.11)
5-min Apgar <7	1755	1.42%	226	1.29%	287	1.63%	**0.02**	**0.0067**	**1.27**	**(1.07–1.52)**	**1.26**	**(1.06–1.50)**
MAS	238	0.19%	21	0.12%	19	0.11%	**0.014**	0.75	0.91	(0.49–1.68)	0.88	(0.47–1.63)
NICU admission (≥24 h)	536	0.43%	54	0.31%	73	0.42%	0.75	0.09	1.35	(0.95–1.93)	1.33	(0.94–1.90)
Instrumental delivery	15 152	12.2%	2145	12.3%	2328	13.3%	**0.0001**	**0.0054**	**1.09**	**(1.03–1.16)**	**1.10**	**(1.03–1.17)**
Emergency cesarean section	13 723	11.1%	2055	11.7%	2974	16.9%	**<0.0001**	**<0.0001**	**1.54**	**(1.45–1.63)**	**1.57**	**(1.48–1.67)**
Admission asphyxia	662	0.53%	54	0.31%	75	0.43%	0.06	0.064	1.39	(0.98–1.97)	1.37	(0.97–1.95)
Adverse neonatal outcome	1189	0.96%	129	0.73%	149	0.85%	0.15	0.23	1.16	(0.91–1.47)	1.14	(0.90–1.44)
Predicted probability	0.2808	0.16	0.3983	0.16	0.3989	0.16	**<0.0001**	0.71				

Group G2 Induction: 289–290									Induction of labor		Induction of labor	
Reference: 289–294	Expectant management		Expectant management		Induction of labor		Before matching	After matching	crude odds ratio		Adjusted #2 odds ratio	
Nulliparous	**65 440**		**9799**		**9783**		*p*-value	*p*-value	OR	(95% CI)	OR	(95% CI)
Perinatal mortality	92	0.14%	11	0.11%	3	0.03%	**0.004**	**0.03**	**0.27**	**(0.08–0.98)**	**0.26**	**(0.07–0.95)**
Stillbirth	57	0.09%	9	0.09	0	0.00%	**0.004**	**0.0027**	N.A.		N.A.	
Neonatal mortality <28 days	35	0.05%	2	0.02%	3	0.03%	0.34	0.65	1.50	(0.25–8.99)	1.48	(0.25–8.93)
5-min Apgar <4	181	0.28%	23	0.23%	29	0.30%	0.72	0.40	1.26	(0.73–2.19)	1.23	(0.71–2.12)
5-min Apgar <7	1332	2.04%	179	1.83%	213	2.18%	0.35	0.08	1.20	(0.98–1.46)	1.18	(0.96–1.47)
MAS	197	0.30%	17	0.17%	15	0.15%	0.01	0.73	0.88	(0.44–1.77)	0.83	(0.41–1.67)
NICU admission (≥24 h)	404	0.62%	38	0.39%	48	0.49%	0.13	0.28	1.27	(0.83–1.94)	1.23	(0.80–1.89)

TABLE 3 (Continued)

Group G2 Induction: 289–290									Induction of labor		Induction of labor	
Reference: 289–294	Expectant management		Expectant management		Induction of labor		Before matching	After matching	crude odds ratio		Adjusted #2 odds ratio	
Instrumental delivery	13443	20.5%	1842	18.8%	1999	20.4%	0.80	**0.004**	**1.11**	**(1.03–1.19)**	**1.11**	**(1.03–1.19)**
Emergency cesarean section	11855	18.1%	1733	17.7%	2526	25.82%	**<0.0001**	**<0.0001**	**1.62**	**(1.51–1.74)**	**1.59**	**(1.49–1.71)**
Admission asphyxia	510	0.78%	41	0.42%	57	0.58%	**0.03**	0.10	1.40	(0.93–2.09)	1.35	(0.90–2.02)
Adverse neonatal outcome	897	1.37%	91	0.93%	106	1.08%	**0.02**	0.28	1.17	(0.88–1.55)	1.14	(0.86–1.51)
Multiparous	**58463**		**7766**		**7782**		***p*-value**	***p*-value**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Perinatal mortality	49	0.08%	12	0.15%	0	0.00%	**0.01**	**0.0005**	N.A.		N.A.	
Stillbirth	32	0.05%	9	0.12%	0	0.00%	**0.04**	**0.0027**	N.A.		N.A.	
Neonatal mortality <28 days	17	0.03%	3	0.04%	0	0.00%	0.13	0.08	N.A.		N.A.	
5-min Apgar <4	46	0.08%	7	0.09%	12	0.15%	**0.03**	0.25	1.71	(0.67–4.35)	1.70	(0.67–4.31)
5-min Apgar <7	423	0.72%	47	0.61%	74	0.95%	**0.03**	**0.01**	**1.57**	**(1.09–2.28)**	**1.56**	**(1.08–2.26)**
MAS	41	0.07%	4	0.05%	4	0.05%	0.55	1.00	1.00	(0.25–4.00)	0.99	(0.25–3.96)
NICU admission (≥24 h)	132	0.23%	16	0.21%	25	0.32%	0.10	0.16	1.56	(0.83–2.93)	1.55	(0.83–2.90)
Instrumental delivery	1709	2.9%	312	4.0%	329	4.2%	**<0.0001**	0.51	**1.06**	**(0.90–1.24)**	1.05	(0.90–1.23)
Emergency cesarean section	1868	3.2%	322	4.2%	448	5.8%	**<0.0001**	**<0.0001**	**1.41**	**(1.22–1.64)**	**1.40**	**(1.21–1.63)**
Admission asphyxia	152	0.26%	13	0.17%	18	0.23%	0.63	0.37	1.38	(0.68–2.82)	1.38	(0.68–2.82)
Adverse neonatal outcome	292	0.50%	38	0.49%	43	0.55%	0.54	0.58	1.13	(0.73–1.75)	1.12	(0.72–1.74)

Note: Adjusted G2 #1 for parity, ART, ethnicity and age. Adjusted #2 for ethnicity, ART, maternal age (except for the mortality outcome because of low numbers). Adverse neonatal outcome = perinatal mortality (stillbirth and neonatal mortality <28 days), and/or 5-min Apgar <4, and/or NICU admission ≥24 h, and/or meconium aspiration syndrome (MAS), and/or admission asphyxia (cooling treatment for asphyxia, and/or ischemic asphyxia, and/or convulsions, and/or intraventricular bleeding, and/or encephalopathy).

Note: Significant values in bold.

Abbreviations: CI, confidence interval; MAS, meconium aspiration syndrome; N.A., not applicable.

TABLE 4 Outcomes of Group 3 induction at 41+4 to 41+5 (291–292 days) vs expectant management until 42+0 (294 days) after propensity score matching.

Group G3 Induction: 291–292			Propensity matched						Induction of labor		Induction of labor	
Reference: 291–294	Expectant Management		Expectant Management		Induction of labor		Before matching	After matching	Crude odds ratio		Adjusted #1 odds ratio	
	57220		15749		15749		72969	31498	OR	(95% CI)	OR	(95% CI)
Total	*N*	%	*N*	%	*N*	%	*p*-value	*p*-value				
Perinatal mortality	67	0.12%	18	0.11%	11	0.07%	0.11	0.19	0.61	(0.29–1.29)	0.61	(0.29–1.29)
Stillbirth	42	0.07%	13	0.08%	4	0.03%	**0.034**	**0.029**	**0.31**	**(0.10–0.94)**	**0.30**	**(0.10–0.93)**
Neonatal mortality <28 days	25	0.04%	5	0.03%	7	0.04%	0.97	0.56	1.40	(0.44–4.41)	1.40	(0.44–4.41)
5-min Apgar <4	99	0.17%	29	0.18%	46	0.29%	**0.003**	**0.049**	1.59	(0.98–2.53)	**1.61**	**(1.01–2.56)**
5-min Apgar <7	884	1.54%	243	1.54%	261	1.66%	0.32	0.42	1.08	(0.90–1.28)	1.08	(0.91–1.29)
MAS	124	0.22%	30	0.19%	26	0.17%	0.21	0.59	0.87	(0.51–1.47)	0.87	(0.51–1.47)
NICU admission (≥24 h)	243	0.42%	55	0.35%	83	0.53%	0.09	**0.02**	**1.52**	**(1.07–2.13)**	**1.52**	**(1.08–2.13)**
Instrumental delivery	7434	13.0%	2180	13.8%	2280	14.5%	**<0.0001**	0.11	1.05	(0.99–1.12)	**1.08**	**(1.01–1.15)**
Emergency cesarean section	6958	12.2%	2124	13.5%	2850	18.1%	**<0.0001**	**<0.0001**	**1.42**	**(1.33–1.51)**	**1.47**	**(1.38–1.57)**
Admission asphyxia	345	0.60%	85	0.54%	84	0.53%	0.31	0.94	0.98	(0.73–1.34)	0.99	(0.73–1.34)
Adverse neonatal outcome	587	1.03%	154	0.98%	160	1.02%	0.91	0.73	1.04	(0.83–1.30)	1.04	(0.83–1.30)
Predicted probability	0.2763	0.154	0.3676	0.1594	0.3683	0.1589	<0.0001	0.68				

Group G3 Induction: 291–292												
Reference: 291–294	Expectant management		Expectant management		Induction of labor		Before matching	After matching	Crude odds ratio		Adjusted #2 odds ratio	
Nulliparous	**31180**		**9644**		**9398**		*p*-value	*p*-value	OR	(95% CI)	OR	(95% CI)
Perinatal mortality	47	0.15%	14	0.15%	9	0.10%	0.21	0.32	0.66	(0.29–1.52)	0.64	(0.28–1.50)
Stillbirth	31	0.10%	10	0.10%	4	0.04%	0.10	0.12	0.41	(0.13–1.31)	0.39	(0.12–1.25)
Neonatal mortality <28 days	16	0.05%	4	0.04%	5	0.05%	0.94	0.71	1.28	(0.34–4.78)	1.27	(0.34–4.73)
5-min Apgar <4	83	0.27%	24	0.25%	40	0.43%	**0.01**	**0.04**	**1.71**	**(1.03–2.84)**	**1.71**	**(1.03–2.84)**
5-min Apgar <7	673	2.16%	186	1.93%	208	2.21%	0.75	0.17	1.15	(0.94–1.41)	1.15	(0.94–1.40)
NICU admission (≥24 h)	191	0.61%	43	0.45%	64	0.68%	0.46	**0.03**	**1.53**	**(1.04–2.26)**	**1.52**	**(1.03–2.23)**
Instrumental delivery	6622	21.2%	1930	20.0%	1982	21.1%	0.76	0.06	1.06	(0.99–1.15)	1.07	(0.99–1.15)

TABLE 4 (Continued)

Group G3 Induction: 291–292												
Reference: 291–294	**Expectant management**		**Expectant management**		**Induction of labor**		**Before matching**	**After matching**	**Crude odds ratio**		**Adjusted #2 odds ratio**	
Emergency cesarean section	6049	19.4%	1858	19.3%	2489	26.5%	**<0.0001**	**<0.0001**	**1.51**	**(1.41–1.62)**	**1.50**	**(1.40–1.61)**
Admission asphyxia	272	0.87%	64	0.66%	68	0.72%	0.16	0.62	1.09	(0.78–1.54)	1.08	(0.77–1.52)
Adverse neonatal outcome	461	1.48%	121	1.25%	127	1.35%	0.37	0.56	1.08	(0.84–1.39)	1.06	(0.83–1.37)
Multiparous	**26040**		**6105**		**6351**		***p*-value**	***p*-value**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Perinatal mortality	20	0.08%	4	0.07%	2	0.03%	0.22	0.39	0.48	(0.09–2.62)	0.48	(0.09–2.64)
Stillbirth	11	0.04%	3	0.05%	0	0.00%	0.10	0.07	N.A.		N.A.	
Neonatal mortality <28 days	9	0.03%	1	0.02%	2	0.03%	0.90	0.58	1.92	(0.17–21.2)	1.91	(0.17–21.1)
5-min Apgar <4	16	0.06%	5	0.08%	6	0.09%	0.37	0.81	1.15	(0.35–3.78)	1.14	(0.35–3.74)
5-min Apgar <7	211	0.81%	57	0.93%	53	0.83%	0.85	0.55	0.89	(0.61–1.30)	0.89	(0.61–1.29)
NICU admission (≥24 h)	52	0.20%	12	0.20%	19	0.30%	0.13	0.25	1.52	(0.74–3.14)	1.50	(0.73–3.10)
Instrumental delivery	812	3.12%	250	4.10%	298	4.69%	**<0.0001**	0.10	1.15	(0.97–1.37)	1.15	(0.97–1.37)
Emergency cesarean section	909	349%	266	4.36%	361	5.68%	**<0.0001**	**0.0007**	**1.32**	**(1.13–1.56)**	**1.32**	**(1.12–1.55)**
Admission asphyxia	73	0.28%	21	0.34%	16	0.25%	0.70	0.35	0.73	(0.38–1.40)	0.72	(0.38–1.39)
Adverse neonatal outcome	126	0.48%	33	0.54%	33	0.52%	0.72	0.87	0.96	(0.59–1.56)	0.95	(0.59–1.54)

Note: Adjusted #1 G3 for parity, ethnicity, late in care and age (except for mortality outcome because of low numbers). Adjusted #2 for ethnicity, late in care, maternal age (except for mortality outcome because of low numbers). Adverse neonatal outcome = perinatal mortality (stillbirth and neonatal death <28 days), and/or 5-min Apgar <4, and/or NICU admission ≥24 h, and/or meconium aspiration syndrome (MAS), and/or admission asphyxia (cooling treatment for asphyxia, and/or ischemic asphyxia, and/or convulsions, and/or intraventricular bleeding, and/or encephalopathy).

Note: Significant values in bold.

Abbreviations: MAS, meconium aspiration syndrome; NICU, neonatal intensive care unit.

Recent RCTs were not designed or powered to stratify their results by parity.[15–17,25] Conversely, our study showed that the CS rate was considerably increased with IOL compared with that with expectant management in both nulliparous and multiparous women. Most observational studies have shown comparable emergency CS rates in nulliparous and multiparous low-risk women.[21,30–32]

In the Netherlands, expectant management in low-risk pregnancies with fetal surveillance is performed according to local, regional or national protocols from 41 to 42 weeks of gestation.[18] This includes assessment of the fetal condition with sonographic examination and electronic fetal monitoring. If IOL is requested by the mother at 41 weeks in a low-risk pregnancy, referral by the midwife to an obstetrician should be made, and labor should be initiated under obstetrician-led care. Moreover, IOL coincides with a considerable increase in emergency cesarean sections, which is particularly important in nulliparous women, with all the disadvantages for subsequent pregnancies.

Based on this and other cohort studies, we suggest that it would be better to perform shared decision-making for induction or waiting in low-risk pregnancies at 41 weeks of pregnancy than routine induction at 41 weeks of gestation.

5 | CONCLUSION

In all two-day groups investigated in this study, IOL reduced stillbirth at 41 weeks but only reduced perinatal mortality at 41+2 to 41+3 compared with expectant management. A greater proportion of infants had low 5-min Apgar scores and more NICU admissions were observed with IOL, especially in nulliparous women. IOL in all two-day groups coincided with elevated emergency CS rates for both nulliparous and multiparous women. The advantages and disadvantages of IOL compared with those of expectant management require special attention when counseling women at 41 weeks of gestation.

AUTHOR CONTRIBUTIONS

This study was designed by ME, AR and CG. AR performed statistical analysis. Data interpretation was performed by AR, ME, AA, JP, CG. ME and AR wrote the draft version of the paper and all authors critically revised the article and approved the final version.

ACKNOWLEDGMENTS

We thank Perined for the provision of the national perinatal registry data.

CONFLICT OF INTEREST STATEMENT

None.

ORCID

Martine Eskes https://orcid.org/0000-0002-7181-8665

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ravelli ACJ, van der Post JAM, de Groot CJM, Abu-Hanna A, Eskes M. Does induction of labor at 41 weeks (early, mid or late) improve birth outcomes in low-risk pregnancy? A nationwide propensity score-matched study. *Acta Obstet Gynecol Scand*. 2023;102:612-625. doi:10.1111/aogs.14536